REMARKS

Applicants respectfully request a four-month extension of time to February 4, 2009 in which to respond. The four-month extension of time fee is charged to the undersigned Attorney's Deposit Account 10-0100. Should additional fees or a credit be associated with this paper, the additional fees or credit can be charged or credited to the undersigned Attorney's Deposit Account 10-0100.

Claim 16 is added.

Applicants respectfully request entry of the attached letter to the European Patent Office, dated August 23, 2003, evidencing the technical contributions of the 2-bleb vaccine of the present invention, including the human clinical data.

The present claims, define a specific 2-bleb mixture, one specific being deficient in PorA, which 2-bleb mixture provides an unexpected improvement over the prior art directed towards sequential administration. The gravamen of the rejection under 35 USC § 103(a) is that insofar as Berthet et al. teaches a bleb component against CU-385 and Vermont et al. teaches a vaccine useful in protection against meningococcal disease, it is allegedly obvious to combine two vaccines into a single multivalent vaccine. This rationale leads to the untenable conclusion that any permutation and combination of useful vaccines inexorably is obvious under 35 USC § 103(a). It is respectfully submitted that the underlying rationale fails to consider the 2-bleb per se vaccine, specific PorA deficiency in one specific bleb in contradistinction to the lack of PorA deficiency in the second specific bleb, and also fails to consider the unexpected improvement and

teaching away from the prior art as evidenced by the attached letter of record in the counterpart EPO application.

Claim 16 makes clear that the specific 2-bleb mixture and pharmaceutical excipient, in and of itself, provides the new and unexpected improvement.

An early allowance is respectfully requested.

Respectfully submitted,

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Enclosure: August 23, 2003 letter to EP0

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23 August 2003

Our ref MJL/B45308 PCT
Your ref .

Please quote our reference on all correspondence

VIA AIRMAIL and FACSIMILE
Fax No: 00 49 89 2399 4465

Dear Sirs,

Re: Written Opinion on PCT/EP03/06094
in the name of GlaxoSmithKline Biologicals S.A. and Instituto Finlay

After speaking to the Examiner over the phone it was decided that applicant would introduce data to show the beneficial technical contribution to the art of the bleb preparations of the present invention. I enclose said human clinical data.

Secondly, the Examiner pointed out the mention of strain CU-385 in document D1. In this regard it should be noted that D1 only mentions this strain as a reference strain to test the sera of the examples generated with different strains (which are not deficient in PorA). On top of not mentioning the beneficial effect of using an OMV in a bleb mixture which is deficient in PorA, D1 also points towards sequential administration of different OMVs (rather than mixtures) as being the preferred embodiment. For instance, at the bottom of page 48 and Figure 8 it is stated that sequential administration was better than mixing different blebs in terms of bactericidal activity against strains CU-385 and 1000.

We would therefore submit that D1 does not provide motivation for mixing a bleb preparation that is deficient in PorA with one that is not deficient.

Yours faithfully,

Michael J. Lubienski
Authorised Representative

Clinical Trial MenB-002

Subjects aged between 12 to 18 years old (n=150 per group) were immunized with a bivalent MenB OMV vaccine (comprising 25µg of each bleb derived from strain CU-385 (B:4:P1.15,19) and NZ-228/98 [a New Zealand epidemic strain B:4:P1.7b,4]) by intramuscular route using two different immunization schedules (0-2-4 months; 0-1-6 months), or with Havrix-Meningitec-Havrix (0-1-6 month immunization schedule) as control (Havrix is a Hepatitis A vaccine, Meningitec only protects against MenC strains). The bactericidal antibody titers to serogroup B Neisseria meningitidis strains were determined using serum bactericidal assays (SBA) using human complement in preimmune (Pre), one month post second injection (P II) and one month post third injection (P III) sera. Responders in P II and P III were defined as subjects with a 4-fold increase in bactericidal antibody titers in post II and post III as compared to titer in Pre sera, respectively. At the PorA serosubtype level, the M687 strain is homologous to the P1.15 OMV, the NZ124 strain is homologous to the P1.4 OMV, while the other strains (B16B6, BZ10, H44/76) are heterologous to the vaccine OMVs. The vaccine gives good homologous protection against the endemic New Zealand strain, but also protects against heterologous strains due to the presence of CU-385 blebs which are deficient in PorA.